

Diazabicyclononene and Tetrahydropyridine Derivatives with a New Side-Chain

The invention relates to novel five-membered heteroaryl derivatives of the general formula (I). The invention also concerns related aspects including processes for the preparation of
5 the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as renin inhibitors in cardiovascular events and renal insufficiency.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves
10 angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT₁ and AT₂. Whereas AT₁ seems to transmit most of the known functions of Ang II, the role of AT₂ is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular
15 diseases. ACE inhibitors and AT₁ blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, 1996, 489-519; Weber M. A., *Am. J. Hypertens.*, 1992, 5, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney*
20 *International*, 1994, 45, 403; Breyer J. A. *et al.*, *Kidney International*, 1994, 45, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, 1994, 28, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, 1988, 84 (Suppl. 3A), 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, 1992, 327, 669).

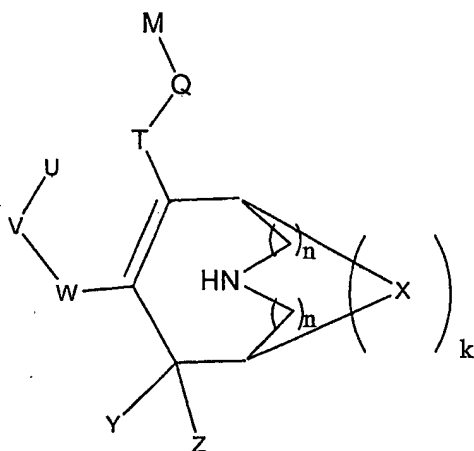
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D.,
25 *Cardiovasc. Drugs*, 1995, 9, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, 1993, 11, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening
30 angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, 1992,

117, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT₁ receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT₂) to Ang II, whose concentration is significantly increased by the blockade of AT₁ receptors. In
5 summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT₁ blockers with regard to efficacy in blocking the RAS and in safety aspects.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, 1994, 12, 419; Neutel J. M. *et al.*, *Am. Heart*, 1991, 122, 1094) has been created with renin inhibitors because of their
10 insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, 1995, 9, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, 2000, 7, 493; Mealy N. E., *Drugs of the Future*, 2001, 26, 1139). Thus, renin inhibitors with
15 good oral bioavailability and long duration of action are required. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, 1999, 6, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il Farmaco*, 2001, 56, 21). However, the development status of these compounds is not known.

20 The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and
25 possibly restenosis. So, the present invention describes these non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula I,



Formula I

wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or

- 5 Y and Z may together form a cyclopropyl ring; in case k represents the integer 1, Y and Z both represent hydrogen;

X represents $-(CH_2)_m-N(L)-(CH_2)_m-$; $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; $-CO-NL-CO-$; $-CO-NL-CHR^6-$; $-CHR^6-NL-CO-$;

- 10 W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$; $-O-CH_2-CH(OCH_3)-CH_2-O-$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-CH_2-O-$; $-O-CH_2-CH(CH_3)-O-$; $-O-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_2CH_2)-O-$; $-O-C(CH_2CH_2)-CH_2-O-$;

A and B independently represent $-O-$; $-S-$; $-SO-$; $-SO_2-$;

- 20 U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or $-COO-$;

Q represents lower alkylene; lower alkenylene;

M represents aryl- $O(CH_2)_vR^5$; heteroaryl- $O(CH_2)_vR^5$; aryl- $O(CH_2)_vO(CH_2)_wR^5$; heteroaryl- $(CH_2)_vO(CH_2)_wR^5$; aryl- $OCH_2CH(R^7)CH_2R^5$; heteroaryl- $OCH_2CH(R^7)CH_2R^5$;

- 25 L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$;

-COCH(Aryl)₂;

K represents -H; -CH₂OR³; -CH₂NR²R³; -CH₂NR²COR³; -CH₂NR²SO₂R³; -CO₂R³; -CH₂OCONR²R³; -CONR²R³; -CH₂NR²CONR²R³; -CH₂SO₂NR²R³; -CH₂SR³; -CH₂SOR³; -CH₂SO₂R³;

5 R¹ represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R² and R^{2'} independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R³ represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; 10 heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -OCOR², -COOR², lower alkoxy, cyano, -CONR²R^{2'}, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -NH(NH)NH₂, -NR⁴R^{4'} or lower alkyl, with the proviso that a 15 carbon atom is attached at the most to one heteroatom in case this carbon atom is sp³-hybridized;

R⁴ and R^{4'} independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -COOR²; -CONH₂;

R⁵ represents -OH, lower alkoxy, -OCOR², -COOR², -NR²R^{2'}, -OCONR²R^{2'}, - 20 NCONR²R^{2'}, cyano, -CONR²R^{2'}, SO₃H, -SONR²R^{2'}, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -NH(NH)NH₂, -NR⁴R^{4'}, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp³-hybridized;

R⁶ represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be 25 unsubstituted or monosubstituted with hydroxy, -CONH₂, -COOH, imidazolyl, -NH₂, -CN, -NH(NH)NH₂;

R⁷ represents -OH, OR²; OCOR²; OCOOR²; or R⁶ and R⁵ form together with the carbon atoms to which they are attached a 1,3-dioxolane ring which is substituted in position 2 with R² and R^{2'}; or R⁶ and R⁵ form together with the carbon atoms to which they are attached a 1,3-dioxolan-2-one ring;

30 k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0; in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0; in case X does not represent -(CH₂)_m-N(L)-(CH₂)_m, n represents the integer 0;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

5 u is the integer 1, 2, or 3;

v is the integer 1, 2, 3, or 4;

w is the integer 1 or 2.

In a preferred embodiment also the following forms are encompassed: optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of
10 diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula I – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain
15 groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of
20 lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

For the substituent R⁸, the term lower alkoxy preferably refers to a methoxy group.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon
25 atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkynyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon
atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens.
30 Examples of lower alkynyl are ethynyl, propynyl or butynyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are methylene, ethylene, propylene or butylene.

For the substituent Q, the term lower alkylene preferably refers to a methylene group.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by
5 halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkyleneoxy** refers to a lower alkylene substituted at one end by an oxygen
10 atom. Examples of lower alkyleneoxy groups are preferably methyleneoxy, ethyleneoxy and propyleneoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring
15 system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkyleneoxy, lower alkylenedioxy, hydroxy, halogen, $-\text{CF}_3$, $-\text{NR}^1\text{R}^{1'}$, $-\text{NR}^1\text{C}(\text{O})\text{R}^{1'}$, $-\text{NR}^1\text{S}(\text{O}_2)\text{R}^{1'}$, $-\text{C}(\text{O})\text{NR}^1\text{R}^{1'}$, lower alkylcarbonyl, $-\text{COOR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{SO}_2\text{NR}^1\text{R}^{1'}$ whereby $\text{R}^{1'}$ represents hydrogen; lower
20 alkyl; lower alkenyl; lower alkynyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl
group; preferably the phenyl group, which can be optionally mono- or multisubstituted by
25 the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkyleneoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NR}^1\text{R}^{1'}$, $-\text{NR}^1\text{R}^{1'}$ - lower alkyl, $-\text{NR}^1\text{C}(\text{O})\text{R}^{1'}$, $-\text{NR}^1\text{S}(\text{O}_2)\text{R}^{1'}$, $-\text{C}(\text{O})\text{NR}^1\text{R}^{1'}$, $-\text{NO}_2$, lower alkylcarbonyl, $-\text{COOR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{SO}_2\text{NR}^1\text{R}^{1'}$, benzyloxy, whereby $\text{R}^{1'}$ has the meaning given above. An example is 2-chloro-3,6-difluorophen-1-yl.

30 For the substituent U, the term aryl means preferably a mono-, di-, or trisubstituted phenyl whereby the substituents are halogen; lower alkyl or lower alkoxy. More preferred it means a mono-, di-, or trisubstituted phenyl whereby the substituents are selected from fluorine and chlorine. A preferred example is 2-chloro-3,6-difluorophen-1-yl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a -COOR² group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequately substituted with lower alkyl, lower alkenyl, lower alkynyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, -CF₃, -OCF₃, -NR¹R^{1'}, -NR¹R^{1'} - lower alkyl, -N(R¹)COR¹, -N(R¹)SO₂R¹, -CONR¹R^{1'}, -NO₂, lower alkylcarbonyl, -COOR¹, -SR¹, -SOR¹, -SO₂R¹, -SO₂NR¹R^{1'}, another aryl, another heteroaryl or another heterocyclyl and the like, whereby R^{1'} has the meaning given above. An example is 3-methyl-pyridinyl, such as 3-methyl-pyridin-4-yl.

For the substituent M, the term heteroaryl means preferably a lower alkyl substituted pyridyl. More preferred it means 3-methyl-pyridinyl. A preferred example is 3-methyl-pyridin-4-yl.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is heteroaryl as defined above.

The term **cycloalkyl - lower alkyl** refers to a cycloalkyl group which is substituted with a lower alkyl group as defined above.

5 The term **aryl - lower alkyl** refers to aryl group which is substituted with a lower alkyl group as defined above.

The term **heteroaryl - lower alkyl** refers to a heteroalkyl group which is substituted with a lower alkyl group as defined above.

10 The term **heterocyclyl - lower alkyl** refers to a heterocyclyl group which is substituted with a lower alkyl group as defined above.

The term **aryloxy - lower alkyl** refers to aryloxy group which is substituted with a lower alkyl group as defined above.

The term **heteroaryloxy - lower alkyl** refers to a heteroaryloxy group which is substituted with a lower alkyl group as defined above.

15 The term **hydroxy - lower alkyl** refers to a lower alkyl group which is substituted with a hydroxyl group.

The term **lower alkylcarbonyl** refers to a -CO-lower alkyl group.

20 The substituent maybe one of the following groups: aryl-O(CH₂)_vR⁸; heteroaryl-O(CH₂)_vR⁸; aryl-O(CH₂)_vO(CH₂)_wR⁸; heteroaryl-(CH₂)_vO(CH₂)_wR⁸; aryl-OCH₂CH(R⁷)CH₂R⁵; heteroaryl-OCH₂CH(R⁷)CH₂R⁵. The aryl or heteroaryl groups are connected to the substituent Q. Examples for aryl are phenyl. Examples for heteroaryl are 3-methyl-pyridin-4-yl, and v is preferably 3. R⁸ is R⁵ as defined above; preferably R⁸ is lower alkoxy (most preferred methoxy). R⁵, R⁷ and w are as defined above.

25 The term **sp³-hybridized** refers to a carbon atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living
30 organisms or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula I can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers

such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

Another preferred embodiment of the invention are compounds of the general formula I, wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or
 10 Y and Z may together form a cyclopropyl ring;

X represents $-\text{CH}_2\text{-CH(K)-CH}_2-$; $-\text{CH}_2\text{CH}_2-$; $-\text{CH}_2\text{OCH}_2-$; $-\text{CH}_2\text{SCH}_2-$; $-\text{CH}_2\text{SOCH}_2-$; $-\text{CH}_2\text{SO}_2\text{CH}_2-$; $-\text{CO-NL-CHR}^6-$; $-\text{CHR}^6\text{-NL-CO-}$;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

15 V represents a bond; $-(\text{CH}_2)_r-$; $-\text{A}-(\text{CH}_2)_s-$; $-\text{CH}_2\text{-A}-(\text{CH}_2)_t-$; $-(\text{CH}_2)_s\text{-A-}$; $-(\text{CH}_2)_2\text{-A}-(\text{CH}_2)_u-$; $-\text{A}-(\text{CH}_2)_v\text{-B-}$; $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-A-CH}_2-$; $-\text{A-CH}_2\text{-CH}_2\text{-B-CH}_2-$; $-\text{CH}_2\text{-A-CH}_2\text{-CH}_2\text{-B-}$; $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-A-CH}_2\text{-CH}_2-$; $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-A-CH}_2-$; $-\text{A-CH}_2\text{-CH}_2\text{-B-CH}_2\text{-CH}_2-$; $-\text{CH}_2\text{-A-CH}_2\text{-CH}_2\text{-B-CH}_2-$; $-\text{CH}_2\text{-A-CH}_2\text{-CH}_2\text{-CH}_2\text{-B-}$; or $-\text{CH}_2\text{-CH}_2\text{-A-CH}_2\text{-CH}_2\text{-B-}$; $-\text{O-CH}_2\text{-CH(OCH}_3\text{)-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-CH(CH}_3\text{)-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-CH(CF}_3\text{)-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-C(CH}_3\text{)}_2\text{-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-C(CH}_3\text{)}_2\text{-O-}$; $-\text{O-C(CH}_3\text{)}_2\text{-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-CH(CH}_3\text{)-O-}$; $-\text{O-CH(CH}_3\text{)-CH}_2\text{-O-}$; $-\text{O-CH}_2\text{-C(CH}_2\text{CH}_2\text{)-O-}$; $-\text{O-C(CH}_2\text{CH}_2\text{)-CH}_2\text{-O-}$;

20 A and B independently represent $-\text{O-}$; $-\text{S-}$; $-\text{SO-}$; $-\text{SO}_2-$;

U represents aryl; heteroaryl;

T represents $-\text{CONR}^1-$; $-(\text{CH}_2)_p\text{OCO-}$; $-(\text{CH}_2)_p\text{N(R}^1\text{)CO-}$; $-(\text{CH}_2)_p\text{N(R}^1\text{)SO}_2-$; or
 25 $-\text{COO-}$;

Q represents lower alkylene; lower alkenylene;

M represents $\text{aryl-O(CH}_2\text{)}_v\text{R}^8$; $\text{heteroaryl-O(CH}_2\text{)}_v\text{R}^8$; $\text{aryl-O(CH}_2\text{)}_v\text{O(CH}_2\text{)}_w\text{R}^8$; $\text{heteroaryl-(CH}_2\text{)}_v\text{O(CH}_2\text{)}_w\text{R}^8$; $\text{aryl-OCH}_2\text{CH(R}^7\text{)CH}_2\text{R}^5$; $\text{heteroaryl-OCH}_2\text{CH(R}^7\text{)CH}_2\text{R}^5$;

L represents $-\text{R}^3$; $-\text{COR}^3$; $-\text{COOR}^3$; $-\text{CONR}^2\text{R}^3$; $-\text{SO}_2\text{R}^3$; $-\text{SO}_2\text{NR}^2\text{R}^3$;

30 $-\text{COCH(Aryl)}_2$;

K represents $-\text{H}$; $-\text{CH}_2\text{OR}^3$; $-\text{CH}_2\text{NR}^2\text{R}^3$; $-\text{CH}_2\text{NR}^2\text{COR}^3$; $-\text{CH}_2\text{NR}^2\text{SO}_2\text{R}^3$; $-\text{CO}_2\text{R}^3$; $-\text{CH}_2\text{OCONR}^2\text{R}^3$; $-\text{CONR}^2\text{R}^3$; $-\text{CH}_2\text{NR}^2\text{CONR}^2\text{R}^3$; $-\text{CH}_2\text{SO}_2\text{NR}^2\text{R}^3$; $-\text{CH}_2\text{SR}^3$; $-\text{CH}_2\text{SOR}^3$; $-\text{CH}_2\text{SO}_2\text{R}^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

5 R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, $-\text{OCOR}^2$, $-\text{COOR}^2$, lower alkoxy, cyano, $-\text{CONR}^2\text{R}^{2'}$, $-\text{CO-morpholin-4-yl}$, $-\text{CO-}((4\text{-loweralkyl})\text{piperazin-1-yl})$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^4\text{R}^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp^3 -hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; $-\text{COOR}^2$; $-\text{CONH}_2$;

15 R^5 represents $-\text{OH}$, lower alkoxy, $-\text{OCOR}^2$, $-\text{COOR}^2$, $-\text{NR}^2\text{R}^{2'}$, $-\text{CONR}^2\text{R}^{2'}$, $-\text{NCONR}^2\text{R}^{2'}$, cyano, $-\text{CONR}^2\text{R}^{2'}$, SO_3H , $-\text{SONR}^2\text{R}^{2'}$, $-\text{CO-morpholin-4-yl}$, $-\text{CO-}((4\text{-loweralkyl})\text{piperazin-1-yl})$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^4\text{R}^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp^3 -hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be
20 unsubstituted or monosubstituted with hydroxy, $-\text{CONH}_2$, $-\text{COOH}$, imidazolyl, $-\text{NH}_2$, $-\text{CN}$, $-\text{NH}(\text{NH})\text{NH}_2$;

R^7 represents $-\text{OH}$, OR^2 ; OCOR^2 ; OCOOR^2 ; or R^6 and R^5 form together with the carbon atoms to which they are attached a 1,3-dioxolane ring which is substituted in position 2 with R^2 and $R^{2'}$; or R^6 and R^5 form together with the carbon atoms to which they are
25 attached a 1,3-dioxolan-2-one ring;

R^8 represents lower alkoxy;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

30 t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 1, 2, 3, or 4;

w is the integer 1 or 2.

Another preferred embodiment of the invention are compounds of the general formula I, wherein X represents $-\text{CH}_2\text{CH}_2-$.

Another preferred embodiment of the invention are compounds of the general formula I, wherein

5 T represents $-\text{CONR}^1-$;

Q represents methylene;

M represents $\text{aryl-O}(\text{CH}_2)_v\text{R}^8$; $\text{heteroaryl-O}(\text{CH}_2)_v\text{R}^8$; $\text{aryl-OCH}_2\text{CH}(\text{R}^7)\text{CH}_2\text{R}^5$; $\text{heteroaryl-OCH}_2\text{CH}(\text{R}^7)\text{CH}_2\text{R}^5$.

Another preferred embodiment of the invention are compounds of the general formula I, wherein

10 R^1 represents cycloalkyl;

R^8 represents lower alkoxy

v represents 3.

Another preferred embodiment of the invention are compounds of the general formula I as defined above, wherein W represents a 1,4-disubstituted pl.

Another preferred embodiment of the invention are compounds of the general formula I as defined above, wherein U is a mono-, di-, or trisubstituted phenyl whereby the substituents are halogen; lower alkyl or lower alkoxy.

Another preferred embodiment of the invention are compounds of the general formula I as defined above, wherein U is a mono-, di-, or trisubstituted phenyl whereby the substituents are selected from fluorine and chlorine.

Another preferred embodiment of the invention are compounds of the general formula I as defined above, wherein V represents $-\text{A}-(\text{CH}_2)_s-$.

Another preferred embodiment of the invention are compounds of the general formula I as defined above, wherein A represents $-\text{O}-$, and s represents 3.

Another preferred embodiment of the invention are compounds selected from the group consisting of

(*rac.*)-(1*R**, 5*S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-methoxypropoxy)-3-methylpyridin-4-ylmethyl]amide.

The invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac

hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, 5 hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, which method comprises administering a compound as defined above to a human being or animal.

In another embodiment, the invention relates to a method for the treatment and/or 10 prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy.

15 In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system as well as for the treatment of the above-mentioned diseases.

The invention also relates to the use of compounds of formula (I) for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

20 A further aspect of the present invention is related to a pharmaceutical composition containing at least one compound according to general formula (I) and pharmaceutically acceptable carrier materials or adjuvants. This pharmaceutical composition may be used for the treatment or prophylaxis of the above-mentioned disorders; as well as for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned 25 diseases.

Derivatives of formula (I) or the above-mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds comprising ACE-inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, 30 sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

In a preferred embodiment, this amount is comprised between 2 mg and 1000 mg per day.

In a particular preferred embodiment, this amount is comprised between 1 mg and 500 mg per day.

In a more particularly preferred embodiment, this amount is comprised between
5 5 mg and 200 mg per day.

All forms of prodrugs leading to an active component comprised by general formula (I) above are included in the present invention.

Compounds of formula (I) and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical compositions containing at least
10 one compound of formula (I) and pharmaceutically acceptable inert carrier material or adjuvants. These pharmaceutical compositions can be used for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of
15 injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and their pharmaceutically acceptable acid addition salts, optionally in combination with
20 other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or
25 its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for
30 example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for

injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case.

Another aspect of the invention is related to a process for the preparation of a pharmaceutical composition comprising a derivative of the general formula (I). According to said process, one or more active ingredients of the general formula (I) are mixing with inert excipients in a manner known *per se*.

The compounds of general formula I can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Preparation of the precursors:

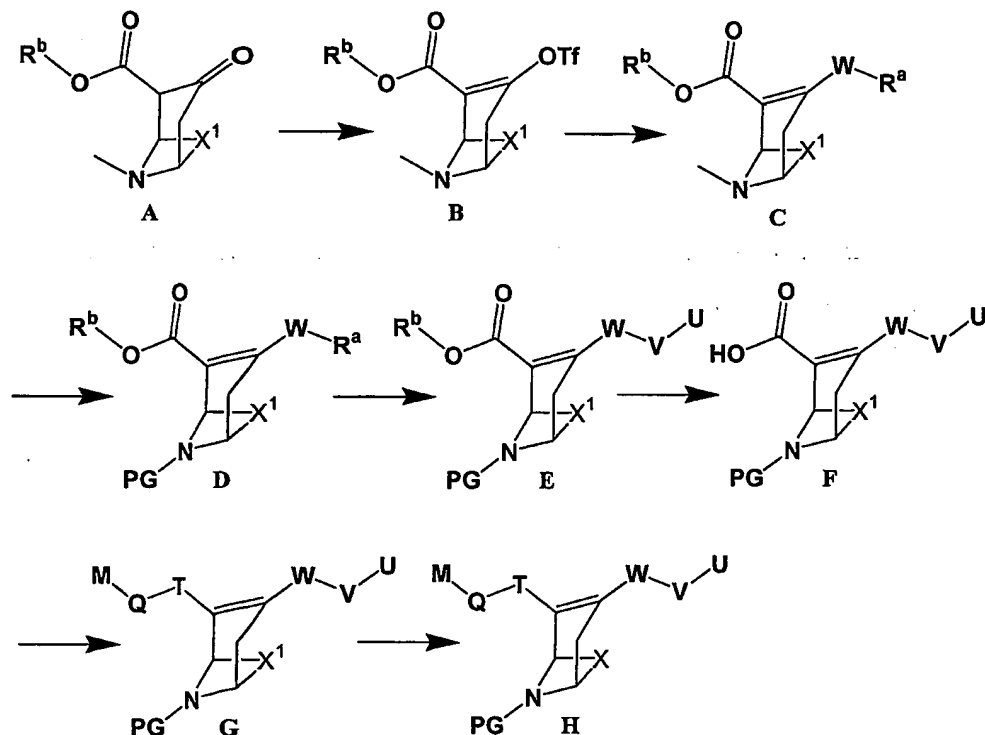
Precursors are compounds which were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry. Most of the chemistry applicable here has already been described in the patent applications WO03/093267 and WO04/002957.

As illustrated in Scheme 1 the known compound A can be derivatised into the corresponding triflate B. X^1 stands for a precursor of the substituent X as defined in general formula (I). The substituent X^1 can be transformed into the substituent X at any stage of the synthesis, whenever convenient. A *Negishi*-type coupling (or any other coupling catalysed by a transition metal) leads to a compound of type C, wherein R^a represents a precursor of the substituent U-V as defined in general formula (I). R^a can be easily transformed into U-V, using elemental chemical steps. After protecting group

manipulation (\rightarrow compound of type D), ajustement of the W-V-U linker is possible for instance by deprotection and a *Mitsunobu*-type reaction, leading to a compound of type E. Hydrolysis of the ester leads to a carboxylic acid of type F, then an amide coupling for instance to a compound of type G. Removal of the Boc-protecting group and alkylation, or

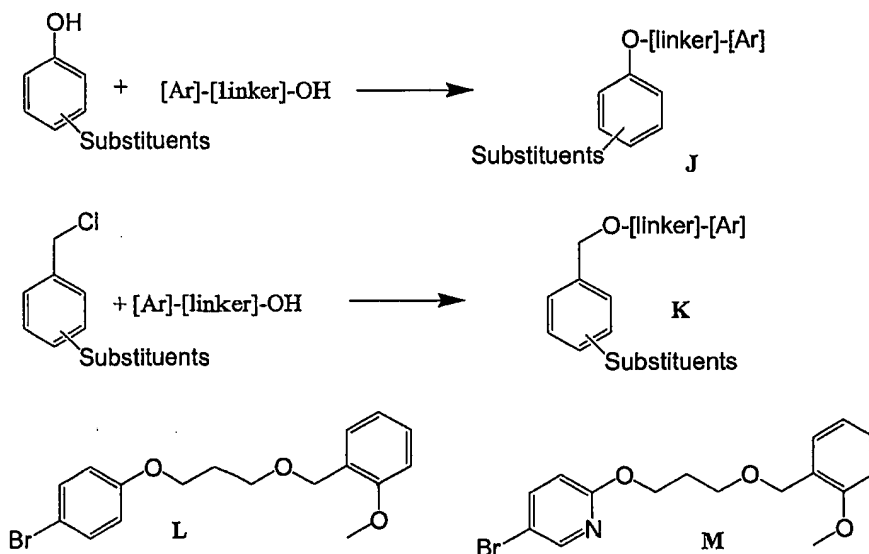
5 acylation, leads to a precursor of type H.

Scheme 1



10 The bromoaryl components can be prepared as described in Scheme 2. A *Mitsunobu* coupling (\rightarrow compounds of type J) or the alkylation of an alcohol with a benzylic chloride (or bromide, \rightarrow compounds of type K) are often the most convenient methods. Derivatives L and M were prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, 1999, 9, 1397) or 3-(5-bromopyridin-2-

15 yloxy)propan-1-ol (Patent Application WO 98/39328) according to these methods. Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, can be used as well (see e.g. March, J, "Advanced Organic Chemistry", 3rd ed., John Wiley and sons, 1985).

16
Scheme 25 Preparation of the secondary amines

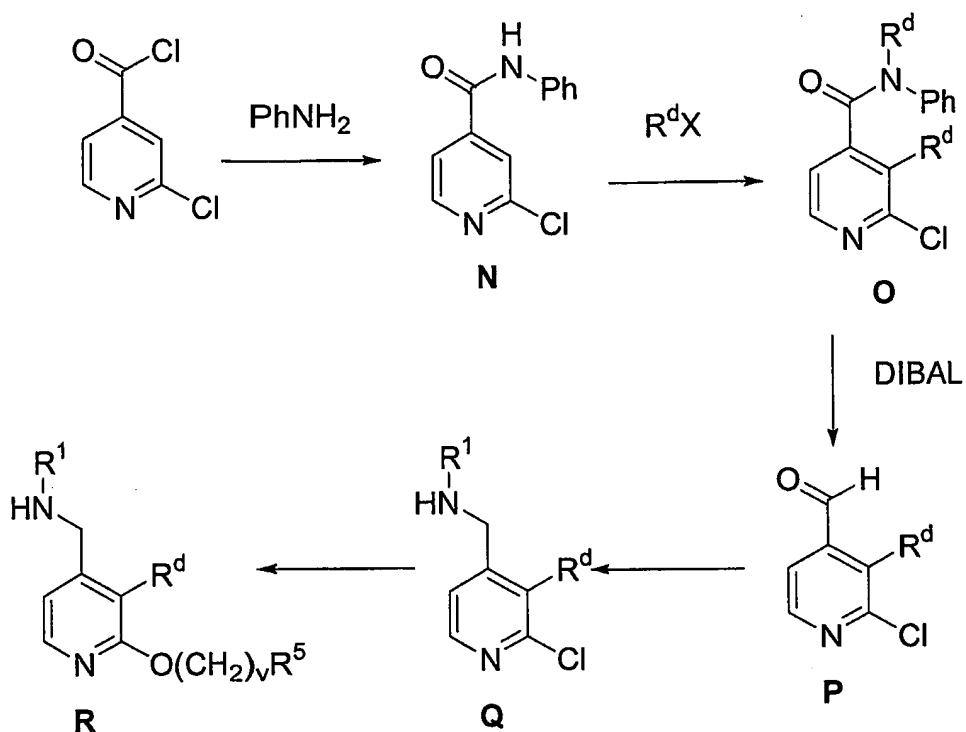
The secondary amines can be prepared for instance as described in Scheme 3. The pyridine derivative **N** can be prepared from commercially available 2-chloro-isonicotinoyl chloride. Deprotonation at the 3-position of this derivative, for instance with BuLi, and subsequent alkylation with a suitable electrophile leads to a derivative of type **O**, wherein

10 R^d represents a suitable substituent that can be introduced by this chemistry, and can be transformed later into a desired substituent as described in general formula I. Reduction of the amide into an aldehyde with DIBAL leads to a compound of type **P**, then a reductive amination leads to an amine of type **Q**, wherein R^1 stand for a substituent as defined above. Finally substitution of the chlorine atom with an alcohol of type $HO(CH_2)_vR^5$, wherein R^5

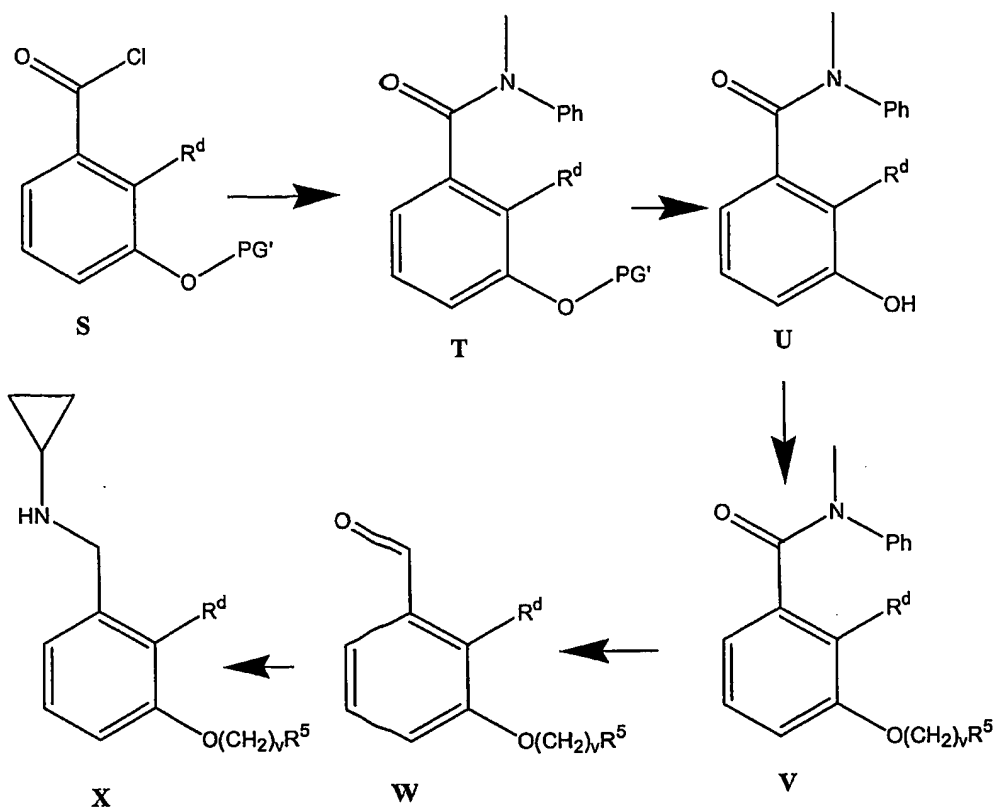
15 may still be protected, leads to an amine of type **R**. An alcohol of type $HO(CH_2)_2O(CH_2)_wR^5$ can be introduced in the same way.

17

Scheme 3



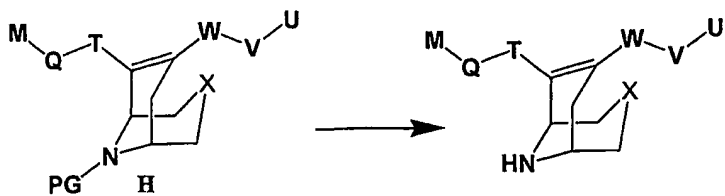
In the case of phenyl derivatives it is better to start from a compound of type **S**, wherein
 5 PG' represents a suitable protecting group. Amide coupling with *N*-methylaniline leads to a derivative of type **T**, then deprotection to a derivative of type **U**. Ether bond formation, via a *Mitsunobu*-type reaction or from a corresponding alkyl halide, leads to a compound of type **V**. Reduction leads to an aldehyde of type **W**, then reductive amination to an amine of type **X**. An alcohol of type $\text{HO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_w\text{R}^5$ can be introduced in the same
 10 way.

18
Scheme 4Preparation of final compounds

- 5 From precursors prepared as described above, the final compounds can be prepared using parallel chemistry techniques. For the specific examples, see the experimental part. Diazabicyclononenes of type of **H** can be deprotected using standard procedures (Scheme 5). Purification by preparative HPLC gives the corresponding TFA salts or formate salts.

10

Scheme 5



- The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

15

ExamplesAbbreviations

	ACE	Angiotensin Converting Enzyme
5	Ang	Angiotensin
	aq.	aqueous
	Boc	<i>tert</i> -Butyloxycarbonyl
	BSA	Bovine serum albumine
	BuLi	<i>n</i> -Butyllithium
10	conc.	concentrated
	DIBAL	Diisobutyl aluminium hydride
	DIPEA	Diisopropylethylamine
	DMAP	4- <i>N,N</i> -Dimethylaminopyridine
	DMF	<i>N,N</i> -Dimethylformamide
15	DMSO	Dimethylsulfoxide
	EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	Enzyme immunoassay
	Et	Ethyl
	EtOAc	Ethyl acetate
20	FC	Flash Chromatography
	HOBt	Hydroxybenzotriazol
	MeOH	Methanol
	org.	organic
	PG	protecting group
25	RAS	Renin Angiotensin System
	rt	room temperature
	sat.	saturated
	sol.	Solution
	TBAF	Tetra- <i>n</i> -butylammonium fluoride
30	TBDMS	<i>tert</i> -Butyldimethylsilyl
	Tf	Trifluoromethylsulfonyl
	THF	Tetrahydrofuran

(rac.)-(1R*, 5S*)-8-Methyl-3-trifluoromethanesulfonyloxy-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (B)

A sol. of compound 8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester (Majewski, M., Lazny, R., *J. Org. Chem.*, 1995, 60, 5825, 1.81 g, 9.12 mmol) in THF
5 (35 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 435 mg, about 10.0 mmol) was added. A gas evolution was observed. After 20 min, Tf₂NPh (3.86 g, 10.8 mmol) was added. 10 min later, the ice bath was removed. The sol. was stirred overnight, and diluted with EtOAc and washed with brine (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by
10 FC yielded the title compound (2.37 g, 78%).

(rac.)-(1R*, 5S*)-3-{4-[3-(tert-Butyldimethylsilyloxy)propyl]phenyl}-8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (C)

A sol. of [3-(4-bromophenyl)propoxy]-tert-butyldimethylsilane (Kiesewetter D. O.,
15 *Tetrahedron Asymmetry*, 1993, 4, 2183, 16.47 g, 50.0 mmol) in THF (250 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 31.0 mL, 50.0 mmol) was added. After 30 min, ZnCl₂ (1M in THF, 52 mL, 52 mmol, prepared from ZnCl₂ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate B (7.90 g, 24.0 mmol) in THF (20 mL) and then Pd(PPh₃)₄ (500 mg, 0.43 mmol) were added. The mixture
20 was heated to reflux for 90 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title product (8.44 g, 82%).

(rac.)-(1R*, 5S*)-3-[4-(3-Hydroxypropyl)phenyl]-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-tert-butyl ester 2-methyl ester (D)

1-Chloroethyl chloroformate (7.98 g, 56.0 mmol) was added to a sol. of bicyclooctene C (8.07 g, 18.8 mmol) in 1,2-dichloroethane (120 mL). The sol. was heated to reflux. After 4 h, the reaction mixture was allowed to cool to rt, and the solvents were removed under
30 reduced pressure. MeOH (100 mL) was added. The mixture was stirred at 75 °C for 30 min, and the solvents were removed under reduced pressure. The residue was diluted with EtOAc and washed with aq. 1M NaOH (2x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dissolved

in CH₂Cl₂ (50 mL), DIPEA (4.70 g, 36.0 mmol) was added, and the mixture was cooled to 0 °C. Boc₂O (4.65 g, 21.0 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.81 g, 64%).

(rac.)-(1*R, 5*S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E)**

Tributylphosphine (1.61 mL, 7.2 mmol) was added to a sol. of bicycloctene **D** (1.04 g, 2.59 mmol), 2-chloro-3,6-trifluorophenol (833 mg, 5.10 mmol) and azodicarboxylic dipiperidide (1.29 g, 5.10 mmol) in toluene (25 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (1.11 g, 78%).

(rac.)-(1*R, 5*S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F)**

Bicycloctene **E** (2.42 g, 4.40 mmol) was dissolved in EtOH (50 mL). Aq. 1M NaOH (40 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (2.48 g, quantitative).

(rac.)-(1*R, 5*S**)-2-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G1)**

To a sol. of compound **F** (3.45 g, 6.46 mmol) in CH₂Cl₂ (60 mL) were added the amine **R** (2.26 g, 6.46 mmol), DMAP (197 mg, 1.62 mmol), DIPEA (4.42 mL, 25.8 mmol), HOBT (1.30 g, 9.69 mmol), and EDC·HCl (3.09 g, 16.2 mmol). The mixture was stirred at rt overnight. EDC·HCl (2.00 g, 1.00 mmol) and DIPEA (3.50 mL, 20.4 mmol) were added. The mixture was stirred at rt for 3 days. Amine **R** (2.00 g, 5.71 mmol), EDC·HCl (2.00 g,

1.01 mmol), and HOBt (1.00 g, 7.40 mol) were added. After 2 days (total 6 days) the mixture was diluted with more CH₂Cl₂, washed with aq. 1M HCl (3x), and with aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7 → 2:4) yielded the title compound (3.43 g, 61%).

(rac.)-(1R*, 5S*)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide (G2)

10 A sol. of compound G1 (3.43 g, 3.95 mmol) in CH₂Cl₂ (35 mL) was cooled to 0 °C. HCl/dioxane (4M, 35 mL) was added. After 15 min the ice bath was removed and the mixture was stirred for 1 h at rt. The solvents were rapidly removed under reduced pressure and the residue was dried under high vacuum for 15 min. The residue was then diluted with CH₂Cl₂ and washed with aq. 1M NaOH (1x). The org. extracts were dried
15 over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 5% → 10% → 15% → 20%) yielded the title compound (1.25 g, 48%).

(rac.)-(1R*, 5S*)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-2-{cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]-carbamoyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G3)

To a sol. of compound G2 (1.19 g, 1.82 mmol) in CH₂Cl₂ (5 mL) was added at 0°C DIPEA (0.80 mL, 4.56 mmol) and Boc₂O (0.61 g 2.74 mmol). The mixture was stirred at 0 °C for 30 min and was concentrated under reduced pressure. Aq. sat. NH₄Cl (5 mL) was added
25 and the mixture was extracted with CH₂Cl₂ (3x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane = 1:1) yielded the title compound (1.09 g, 80%).

(rac.)-(1R*, 5S*)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-2-{cyclopropyl-[2-(3-methoxypropoxy)-3-methylpyridin-4-ylmethyl]-carbamoyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G4)

30 To a sol. of compound G3 (100 mg, 0.133 mmol) in DMF (2 mL) was added NaH (60% in oil, 96 mg, 0.22 mmol) at 0°C under N₂, and the mixture was stirred for 1 h. MeI (22 µL,

0.133 mmol) was added and the mixture was stirred overnight. Water was added, and the mixture was extracted with CH₂Cl₂ (3x), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1) yielded the title compound (102 mg, 49%).

5

2-Chloro-N-phenylisonicotinamide (N)

To the sol. of 2-chloro-isonicotinoyl chloride (Anderson, W. K., Dean, D. C., Endo, T., *J. Med. Chem.*, **1990**, *33*, 1667, 10 g, 56.8 mmol) in 1,2-dichloroethane (100 mL) was added at 0 °C a sol. of aniline (5.70 mL, 62.5 mmol) and DIPEA (10.2 mL, 59.6 mmol) in 1,2-dichloroethane (10 mL) during ca. 30 min. The reaction was stirred at 0 °C for ca. 30 min and subsequently for 1 h at 95 °C. Water (30 mL) was added at rt and the mixture was filtered-off. The filtrate was extracted with CH₂Cl₂ (200 mL). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was crystallized from MeOH/water 1:10 (110 mL), yielding the title compound (12.12 g, 92%). LC-MS: R_T = 0.87 min; ES⁺ = 233.1.

15

2-Chloro-3-N-dimethyl-N-phenylisonicotinamide (O)

To a sol. of compound N (8.79 g, 37.8 mmol) in THF (90 mL) was added BuLi (1.6M in hexane, 52 mL, 83.2 mmol) at -78 °C. After 30 min MeI (7.70 mL, 124 mmol) was added dropwise at the same temperature. The mixture was stirred at -78 °C for 1 h, and was warmed up to 33 °C. The mixture was stirred at 33 °C for 30 min. Aq. 10% NH₄OH was added dropwise at rt, and the mixture was extracted with Et₂O. The org. extracts were dried over MgSO₄, filtered, and the solvents were evaporated under reduced pressure. Purification by FC yielded the title compound (8.67 g, 88%). LC-MS: R_T = 0.85 min; ES⁺ = 261.2.

25

2-Chloro-3-methylpyridine-4-carbaldehyde (P)

To the sol. of pyridine derivative O (9.58 g, 36.7 mmol) in CH₂Cl₂ (190 mL) was at -78 °C added DIBAL (1M in CH₂Cl₂, 55.1 mL, 55.1 mmol), and the mixture was stirred at -78 °C for 1.5 h. Aq. sat. tartaric acid monosodium monokalium salt in water (20 mL) was added and the mixture was allowed to warm up to rt. Water was added and the mixture was extracted with CH₂Cl₂. The org. extracts were dried over MgSO₄, filtered, and the solvents

30

were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.4 g, 77%). LC-MS:R_T = 0.76 min; ES⁺ = 156.1.

(2-Chloro-3-methylpyridin-4-ylmethyl)-cyclopropylamine (Q)

- 5 A sol. of aldehyde P (4.70 g, 30.2 mmol) and cyclopropylamine (4.20 ml, 60.4 mmol) in MeOH (65 mL) was stirred at rt for 4 h. NaBH₄ (1.55 g, 39.2 mmol) was added and the mixture was stirred at rt for 12 h. Water and subsequently aq. 1M NaOH were added, and the solvents were partially removed under reduced pressure. The water phase was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over MgSO₄, filtered,
10 and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title compound (4.66 g, 79%). LC-MS:R_T = 0.43 min; ES⁺ = 197.1.

{2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methylpyridin-4-ylmethyl}-cyclopropylamine (R)

- 15 A sol. of amine Q (1.24 g, 6.30 mmol) and 2-(*tert*-butyldimethylsilanyloxy)-propan-1-ol (403 mg, 10.1 mmol) in dioxan (5 ml) was heated at 115 °C for 12 h. The solvents were removed under reduced pressure, water was added, and the mixture was extracted with Et₂O (2x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title
20 compound (192 mg, 9%). LC-MS:R_T = 0.84 min; ES⁺ = 351.4.

Example 1

- (*rac.*)-(1*R**, 5*S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-methoxy-propoxy)-3-methylpyridin-4-ylmethyl]amide**
25

A sol. of compound G4 (50 mg) was stirred under N₂ in a sol. HCl in Et₂O (2M, 2 mL) at rt overnight. The reaction mixture was concentrated and crude product was purified by FC (CH₂Cl₂ /MeOH = 9/1), which yielded the title compound (23 mg, 53 %).

- 30 The following assay was carried out in order to determine the activity of the compounds of general formula I and their salts.

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 μ L per well of an enzyme mix and 2.5 μ L of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

- human recombinant renin (0.16 ng/mL) • synthetic human angiotensin(1-14) (0.5 μ M)
- hydroxyquinoline sulfate (1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 μ L of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 μ L of Ang I-antibodies in assay buffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2,2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC₅₀). The IC₅₀-values of all compounds tested are below 10 μ M.

Examples of inhibition:

Example 1: 0.79 nM